

AD _____

CONTRACT NUMBER DAMD17-96-C-6126

TITLE: Signal Enhancement Ratios (SERs) in Breast Carcinomas
Measured by 3D Contrast-MRI and Verified by Histopathology

PRINCIPAL INVESTIGATOR: Nola Hylton, Ph.D.

CONTRACTING ORGANIZATION: University of California
San Francisco, California 94143-0962

REPORT DATE: October 1998

TYPE OF REPORT: Annual

PREPARED FOR: Commander
U.S. Army Medical Research and Materiel Command
Fort Detrick, Frederick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are
those of the author(s) and should not be construed as an official
Department of the Army position, policy or decision unless so
designated by other documentation.

DTIC QUALITY INSPECTED 4

19990810 054

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED	
	October 1998	Annual (27 Sep 97 - 26 Sep 98)	
4. TITLE AND SUBTITLE		5. FUNDING NUMBERS	
Signal Enhancement Ratios (SERs) in Breast Carcinomas Measured by 3D Contrast-MRI and Verified by Histopathology		DAMD17-96-C-6126	
6. AUTHOR(S)		8. PERFORMING ORGANIZATION REPORT NUMBER	
Nola Hylton, Ph.D.			
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)		9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	
University of California San Francisco, California 94143-0962		Commander U.S. Army Medical Research and Materiel Command Fort Detrick, Frederick, Maryland 21702-5012	
10. SPONSORING/MONITORING AGENCY REPORT NUMBER			
11. SUPPLEMENTARY NOTES			
12a. DISTRIBUTION / AVAILABILITY STATEMENT		12b. DISTRIBUTION CODE	
Approved for public release; distribution unlimited			
13. ABSTRACT (Maximum 200)			
Our work in breast MRI has focused on an imaging technique and analysis method, directed toward defining the extent of malignant lesions in patients with confirmed breast carcinoma. We developed a 3-point contrast-MRI method to maximize anatomic (sensitivity) and biologic (specificity) information in a single exam. One data set is acquired at baseline (pre-contrast), S_0 ; one early post-contrast, S_1 ; and one late post-contrast, S_2 . The SER index, defined as $(S_1 - S_0) / (S_2 - S_0)$, compares early to late enhancement. Preliminary studies suggested a relationship between SER value and tumor grade for invasive carcinomas. Our overall objective has been to develop and characterize this technique to be used with both high diagnostic and staging accuracy in evaluating the breast. Both the data acquisition and image analysis techniques are straightforward. We have aimed to reduce the computational complexity and to develop automated algorithms for analysis that can reduce inter- and intra-observer variability in making diagnostic and staging assessments. Our performance assessments to date demonstrate a 25% specificity improvement for this 3-time point method compared to a 'static' (2-point) method, approaching or exceeding specificity improvements reported with dynamic imaging techniques. Our staging results show that MRI performs substantially better than mammography in demonstrating disease extent, particularly in cases of multi-focal cancer and ductal carcinoma in situ. These results suggest that MRI may be cost-effective when used pre-surgically.			
14. SUBJECT TERMS		15. NUMBER OF PAGES	
Breast Cancer magnetic resonance imaging (MRI), high resolution, contrast dynamics histopathology, local staging, angiogenesis		9	
		16. PRICE CODE	
17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

Where copyrighted material is quoted, permission has been obtained to use such material.

Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

MA In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

MA For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.


PI - Signature

11.23.98
Date

TABLE OF CONTENTS

Cover	Page 1
Form SF 298	Page 2
Foreword	Page 3
Table of Contents	Page 4
Introduction	Page 5
Body	Page 5
Conclusions	Page 7
References	Page 8

ANNUAL REPORT FOR CONTRACT NUMBER DAMD17-96-C-6126

Project Period September 27, 1997 – September 26, 1998

Principal Investigator: Nola Hylton, Ph.D., University of California, San Francisco

Grant Title: Signal Enhancement Ratios (SERs) in Breast Carcinomas Measured by 3D Contrast-MRI and Verified by Histopathology

INTRODUCTION

Our work in breast MRI has focused on an imaging technique, the triple acquisition rapid gradient echo technique (TARGET), and signal enhancement ratio (SER) analysis method, directed toward defining the extent of malignant lesions in patients with confirmed breast carcinoma. We developed a 3-point contrast-MRI method to maximize anatomic (sensitivity) and biologic (specificity) information in a single exam. Previously reported methods have relied on separate imaging strategies for maximizing sensitivity and specificity¹⁻¹². TARGET acquires one data set at baseline (pre-contrast), S_0 ; one early post-contrast, S_1 ; and one late post-contrast, S_2 . The SER index, defined as $(S_1 - S_0) / (S_2 - S_0)$, compares early to late enhancement: SER values less than one indicate breast tissue that enhances gradually; SER values equal to one indicate breast tissue enhancement that is stable between the early and late post-contrast time points; SER values greater than one indicate breast tissue demonstrating uptake with contrast washout by the late time point¹³⁻¹⁵. In the preliminary data provided in our original grant application, we presented results in a group of 25 patients with pathology confirmation. MRI correctly identified carcinoma in 21/25 cases using a two-point comparison only: percent enhancement (PE) = $(S_1 - S_0) / S_0 > 80\%$. The one false positive was resolved when SER>1.2 was used as an additional criteria for malignancy. Of particular interest, these preliminary studies also suggested a relationship between SER value and tumor grade in the group of 18 invasive carcinomas.

The focus of this grant has been to verify these findings in a larger population of patients with confirmed breast carcinoma, and investigate the potential of SER as a non-invasive prognostic marker.

BODY

Experimental Methods, Assumptions and Procedures: 50 women subjects per year are enrolled in this research protocol and receive one breast MRI exam prior to undergoing surgery. Study eligibility include women with a confirmed breast carcinoma on the basis of fine needle aspiration (FNA), core biopsy, excisional biopsy, or lumpectomy with positive margins. The MRI procedure is performed on a General Electric 1.5 Tesla SIGNA scanner using a bilateral phased-array breast radiofrequency coil. The imaging exam consists of a bilateral, axial T1-weighted, spin echo localization scan, a sagittal, fat-suppressed T2-weighted fast spin echo scan of the symptomatic breast only, and a contrast-enhanced TARGET series of the symptomatic breast only, using a 3D fat-suppressed, fast gradient echo technique: TR = 11 ms, TE = 4.2 ms, 20 degree flip angle, 256 x 192 imaging matrix, 16-18 cm field of view, 60 sections, 2 NEX and no phase wrap option. The scan time for each data acquisition is 5.4 minutes, resulting in a three-point temporal sampling of 0, 2.7 and 8.1 minutes. Gadolinium-DTPA is administered intravenously through an indwelling catheter at a dose of 0.1 mmol/kg body weight, following the first scan of the TARGET series.

Software and hardware upgrades to our General Electric Signa scanner have allowed us to decrease the TR of the 3D pulse sequence to 8.7 ms, maintaining all other parameters constant. The resulting scan time is 5:00 minutes, resulting in a new temporal sampling of 0, 2.5 and 7.5 minutes. This change was made in August 1998, following the accrual of 178 patients. We intend to compare the performance in the two subsets of patients scanned before and after the change in temporal resolution.

Following each patient exam, MRI image data are transferred off-line to a UNIX workstation for processing and analysis. Maximum intensity projections and region-of-interest calculations are performed to measure peak PE and SER values in the area of suspicion based upon the patient's reason for referral. Additional areas of suspicion and incidental MRI findings are also characterized.

Tissue tracking and histopathology correlation procedures were developed in Year I and continue to be used in this study.

Results and Discussion: We have accrued an additional 63 patients into our study. Our combined patient database now has over 300 patient entries, including the patients generated from this study. We performed a study to evaluate the value of low temporal resolution kinetic information gained by the three-time point method of data acquisition. We compared a two-point method considering PE only to a three-point method combining PE and SER thresholds, for sensitivity and specificity. Thresholds were separately optimized in each case using receiver operating characteristic (ROC) curve analysis and requiring a minimum sensitivity of 95%. A specificity increase from 42 to 67% was found using the three-point method, in comparison to the two-point method. These results will be presented at the RSNA in December 1998 and have been submitted for publication¹⁶.

We evaluated the correlation of SER value and grade, and SER value and microvessel density (MVD) in a group of 57 patients with confirmed carcinoma and subsequent surgical pathology confirmation. SER correlation with microvessel density counts (by CD 34 staining) was highly significant, $r = 0.62$ ($p < 0.002$). The correlation between SER and grade (by SBR number) was $r = 0.59$ ($p < 0.004$). SER increased with the grade of tumor, showing greatest separation between tumors of grade 2 and 3. These results have been accepted for publication¹⁷.

In an evaluation of staging accuracy, tumor extent was measured on MRI and mammography and their concordance with pathology was compared. In a group of 45 patients with carcinoma and MRI and mammography taken at comparable times, carcinoma was correctly identified by MRI in 98% of cases, versus 84% for mammography. True anatomic extent was correctly identified much more often with MRI than with mammography (96% vs. 44%), with the greatest value in cases of multi-focal disease, ductal carcinoma in situ (DCIS), or invasive carcinoma with an extensive intraductal component (EIC)¹⁸.

In our Statement of Work, we estimated that Tasks 4-5 under Specific Aim 1 would be accomplished during Year 2, and Task 2 under Specific Aim 2 would be partially underway. These tasks were as follows:

SPECIFIC AIM 1 (Determine the histologic basis for interpreting SER patterns)

Task 4: Assess registration accuracy in patients studies to date. Realign and reevaluate SER results as needed.

Task 5: Analyze SER/grade and SER vessel count data; Use results to reclassify SER ranges for improved segmentation. Perform retrospective analysis of studies to date.

SPECIFIC AIM 2 (Investigate the possible prognostic value of SER characteristics)

Task 2: Develop software to facilitate SER analysis and generation of illustrations and reports for pre-surgical review.

We had made substantial progress in each of these areas. **Specific accomplishments** during the second year have been:

- We have advanced our image analysis capabilities by developing a minimally-supervised algorithm for tumor analysis. Input from the user involves placing two regions of interest enclosing the

areas of suspicion on orthogonal projection views generated by maximum intensity projection of the contrast-enhanced data. The software program analyzes the defined volume to generate tumor volume calculations, mean peak percent enhancement (PE) and signal enhancement ratio (SER) values, and segmented tumor volumes by SER ranges. In a comparison of 57 cases including a range of pathologies, equivalent sensitivity and specificity were measured by the manual and semi-automated methods, with a time reduction of approximately 45 minutes using the manual method, to 5 minutes for the semi-automated method. One limitation of the semi-automated method is the requirement that the data be registered. We have found patient coaching, prior to the exam to be very successful in avoiding patient motion. The goal of this work has been to provide an efficient and accurate method for image analysis and data reduction. An abstract and paper proceeding will be presented at the 'Medicine Meets Virtual Reality: 7 meeting to be held January 20-23, 1999 in San Francisco, CA¹⁹.

- In seventeen patients undergoing MRI exams before and after neoadjuvant chemotherapy, semi-automatic analysis was used to measure changes in tumor volume and SER. Stratifying patients by the percent change in volume by MRI, we have found that in all cases of tumor reduction of 75% or more, there was an associated reduction in SER, with an average reduction of 31%. In the range of 25% to 75% volume reduction, 70% of patients showed an SER reduction, however 30% showed an increase. Only one patient was found to have a volume reduction of less than 25%, and showed an SER decrease of 13%. These data are preliminary and the study is ongoing. We are also now evaluating patients following a single cycle of chemotherapy to evaluate whether there is an early predictive value of SER response. Follow-up will be required to determine if an association exists between MRI measurements of volume and SER response and the likelihood of recurrence in this population.
- In a subset of 128 patients, we have demonstrated a specificity improvement of 25% over conventional high resolution techniques, using the three time point method that we have developed. These results will be presented at the RSNA in December 1998 and have been submitted for publication¹⁶.
- Results describing the correlation of tumor SER and microvessel density were accepted for publication¹⁷.
- Results describing comparing the staging accuracy of MRI and mammography were accepted for publication¹⁸.

CONCLUSIONS

Our overall objective has been to develop and characterize a high resolution contrast-enhanced MRI technique that can be used with both high diagnostic and staging accuracy in evaluating the breast. Both the data acquisition and image analysis techniques are straightforward. We have aimed to reduce the computational complexity of this technique and to develop automated algorithms for analysis that can reduce inter- and intra-observer variability in making diagnostic and staging assessments. Our performance assessments to date show that this method performs with improved specificity in comparison to other 'static' high resolution contrast-enhanced techniques of the breast, and approaches or exceeds specificity values reported with dynamic imaging techniques. Our staging results also suggest that MRI may be cost-effective when used pre-surgically.

REFERENCES

1. Heywang SH, Wolf A, Pruss E, et al. *MR Imaging of the Breast with Gd-DTPA: Use and Limitations*. Radiology 1989; 171:95-103.
2. Kaiser WA, Zeitler E. *MR Imaging of the Breast: Fast Imaging Sequences with and without Gd-DTPA Preliminary Observations*. Radiology 1989;170:681-686.
3. Flickinger FW, Allison JD, Sherry RM, Wright JC. *Differentiation of Benign From Malignant Breast Masses By Time-Intensity Evaluation of Contrast-Enhanced MRI*. Magn Reson Imag. 11:617-620, 1993.
4. Heywang SH, Hilbertz T, Pruss E, et al. *Dynamische kontrastmitteluntersuchungen mit FLASH bei kernspintomographie der mamma*. Digitale Bildiagn 1988; 8:7-13.
5. Gilles R, Guinebretiere JM, Lucidarme O, Cluzel P, Janaud G, Finet JF, Tardivon A, Masselot J, Vanel D. *Non-palpable Breast Tumors: Diagnosis with Contrast-enhanced Subtraction Dynamic MR Imaging*. Radiology 1994; 191:625-631.
6. Turkat TJ, Klein BD, Polan RL, Richman RH. *Dynamic MR Mammography: A Technique for Potentially Reducing the Biopsy Rate for Benign Breast Disease*. J Magn Res Img 1994; 4:563-568.
7. Gilles R, Meunier M, Lucidarme O, Zafrani B, Guinebretiere JM, Tardivon AA, Le Gal M, Vanel D, Neuenschwander S, Arriagada R. *Clustered Breast Microcalcifications: Evaluation by Dynamic Contrast-Enhanced Subtraction MRI*. J Comp Assis Tomog. 1996; 20(1):9-14.
8. Boetes C, Barentsz JO, Mus RD, van der Sluis RF, van Erning LJTO, Hendriks JHCL, Holland R, Ruys SHJ. *MR Characterization of Suspicious Breast Lesions with a Gadolinium-Enhanced TurboFLASH Subtraction Technique*. Radiology 1994; 193:777-781.
9. Pierce WB, Harms SE, Flamig DP, Griffey RH, Evans WP, Hagans JE. *Three-dimensional Gadolinium-enhanced MR Imaging of the Breast: Pulse Sequence with Fat Suppression and Magnetization Transfer Contrast. Work-in-Progress*. Radiology 1991; 181:757-763.
10. Harms SE, Flamig DP, Hesley KL, et al. *MR Imaging of the Breast with Rotating Delivery of Excitation Off Resonance: Clinical Experience with Pathologic Correlation*. Radiology 1993; 187:493-501.
11. Oellinger H, Heins S, Sander B, et al. *Gd-DTPA Enhanced MR Breast Imaging: The Most Sensitive Method for Multicentric Carcinomas of the Female Breast*. Euro Rad, 1993.
12. Cross MJ, Harms SE, Cheek JH, Peters GN, Jones RC. *New Horizons in the Diagnosis and Treatment of Breast Cancer Using Magnetic Resonance Imaging*. Am J. of Surg. 1993; 166:749-755.
13. Hylton NM, Foo TKJ, Frankel SD, Esserman LJ, Shimakawa A, Proctor E, Bruce N, Sickles E. *Optimization of a Magnetization-Prepared 3D Fast Gradient Echo Technique for Local Staging of Breast Cancer*. Proceedings of the Third Scientific Meeting of the Society of Magnetic Resonance. 1995; 3:1595.
14. Hylton NM, Frankel SD, Esserman LJ, Moore K, Sickles E. *High Resolution 3D Maps of Contrast Enhancement Patterns in Breast Tumors*. Proceedings of the Third Scientific Meeting of the Society of Magnetic Resonance. 1995; 1:439.

15. Hylton NM, Frankel SD, Esserman LJ, Sickles EA. High Spatial Resolution MR Imaging Enhancement Patterns in Breast Malignancies: Usefulness in Distinguishing Invasive from Non-Invasive Carcinoma. *Radiology* 1995; 197(P):371.
16. Hylton NM, Esserman LJ, Partridge SC, Schwerin EH, Wang WL, Weidner N, Barclay J, Sickles EA. *High Resolution Breast MRI using a Three-Point Method.* (submitted)
17. Esserman LJ, Hylton NM, George T and Weidner N. Contrast-enhanced magnetic resonance imaging to assess tumor histopathology and angiogenesis in breast cancer. *The Breast Journal.* (in press)
18. Esserman LJ, Hylton NM, Yassa L, Frankel S and Weidner N. *Utility of MRI in the management of breast cancer: evidence for improved preoperative staging.* *Journal of Clinical Oncology* (in press)
19. Partridge SC, Heumann EJ, Hylton NM. *Semi-Automated Analysis for MRI of Breast Tumors.* Proceedings of the Medicine Meets Virtual Reality:7 Meeting, San Francisco, CA, January 20-23, 1999.